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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/818,954	03/27/2001	Christopher J.R. Paszty	A-676B	9125

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EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/818,954	PASZTY ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10,11,47-51,61 and 65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10,11,47-51,61 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/15/02, 9/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The rejection of claims over US2003/0059877 is withdrawn; the instant application taught at least as much as the reference, prior to the reference's effective date.

The declaration under 37 CFR 1.132 filed 9/17/2004 (The Paszty declaration) is sufficient to overcome the rejection of claims 6, 8, and 48-50 over Mahairas et al. in view of Sibson et al., because it is correctly pointed out that Sibson discusses cDNA, whereas the clone of Mahairas is genomic.

Claim Objections

Claim 8 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim can depend from multiple other claims in the alternative only. Claim 8 depends from claims 1, 2 or 3, *and* claim 8. See MPEP § 608.01(n). Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 10, 11, 47-51, 61 and 65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims that recite specific stringent conditions, such as claims 1-3, remain indefinite because the metes and bounds of what will be obtained via such hybridization are at least as dependent upon the wash conditions (time and buffers) as they are upon the actual hybridization conditions. It is noted that applicants have amended the claims to introduce specific hybridization conditions to overcome the previous rejection, however, such amendment does not adequately resolve the issue.

Claim 2 as amended is indefinite at part (d) of the claim for referring inclusively to parts (a)-(c) of the claim. The dependence from those portions of the claim should not be inclusive, but rather in the alternative. Claim 3 is similarly indefinite at part (f).

Claim 3 remains further indefinite for failing to adequately point out that which applicant sees as the invention. There is no upper limit to the number of substitutions, insertions, deletions, or truncations, such that there is no requirement for any structural similarity to the disclosed nucleic acids. Applicants traversal that the specification provides 'ample disclosure to allow one skilled in the art to determine appropriate substitutions" etc. has been fully considered but is not deemed persuasive. This is not an enablement rejection, but rather a rejection under 35 U.S.C. § 112, second paragraph on the basis that the metes and bounds of the claims cannot be determined. As claim 3 has no limits on the number of changes, one of ordinary skill in the art would not be able to determine whether a given protein did or did not fall within the metes and bounds of the claim, and the claim fails to point out with particularity that which is the disclosed invention. If applicants argument is intended to indicate that the claim is intended to cover all functional equivalents of SEQ ID NO: 1, then such would support the basis of the rejection under 35 U.S.C. §112, first paragraph, as the claim as thus interpreted is a single means claim.

Claim 10 is indefinite as there is no antecedent basis for "the β10 polypeptide" in any of the claims from which it depends, due to the amendments to the claims.

Claim 65 is indefinite for depending from a cancelled claim.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 10, 11, 47-51, 61 and 65 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid of SEQ ID NO: 2 or that encodes SEQ ID NO: 1, does not reasonably provide enablement for the breadth of the claims, which encompass numerous fragments, derivatives, etc. of such. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of this invention is the discovery of two new glycoprotein hormone subunits, designated α2 and β10 by applicants, and α2 and β5 by Nakabayashi et al. The state of the art is that the glycoprotein hormone family was previously known to comprise four members, LH, FSH, hCG, and TSH, which are heterodimeric proteins that share a common α subunit. It was also known in the art, as summarized by Nakabayashi et al., that the effect of structural alterations in the glycoprotein hormones is not predictable (see page 1451, second column). Further, Nakabayashi et al., which is not prior art, but is art subsequent to the filing date of this application, disclose that "a heterodimer consisting of the known α and new β5 subunits did not activate the TSH receptor, and the A2/CGβ heterodimer did not activate the LH receptor." Therefore, Nakabayashi et al. teach that the newly identified glycoprotein hormone differs substantively from the previously known four species, in that its subunits may *not* be interchanged with those of the other known family members. Thus, the art evidences a lack of predictability in making alterations to glycoprotein hormones in general, and α2/β10 in particular.

The claims are extremely broad. The specification discloses a single species of protein, having a particular amino acid sequence. However, the claims encompass nucleic acids that hybridize under ill-specified conditions to the disclosed sequence or to degenerate variants of said sequence, nucleic acids encoding proteins having as little as 75% identity to the protein of SEQ ID NO: 1 and are "capable of regulating thyroidal function or promoting thyroid differentiation or proliferation" allelic and splice variants, fragments of any of the above nucleic

acids without regard to any function whatsoever, and nucleic acids encoding proteins with unlimited substitutions, deletions, insertions, truncations. The specification provides no working examples other than the single disclosed protein sequence for each of the two subunits, and provides merely general, non-specific guidance as to alterations that might be made, with no specific direction as applied to the particularly disclosed proteins. Further, there is not disclosure of any splice or allelic variants.

Accordingly, the Examiner concludes that while the specification enables one to make and use the nucleotide sequence of SEQ ID NO: 2 of that which encodes SEQ ID NO: 1, it would require undue experimentation to make and use the invention in a manner commensurate in scope with the claims.

Regarding guidance in the specification as to "capable of regulating thyroidal function or promoting thyroid differentiation or proliferation", the specification provides guidance to such by way of analogy to TSH. For Example, at page 10 the specification states: In addition, diagnostic tests for measuring TSH levels in the blood are commonly used for determining the functional status of the thyroid gland when thyroid gland disorder is suspected. It is likely that human α2/β10 will have similar clinical utilities as TSH and will be useful for the treatment and diagnosis of thyroid gland related diseases and disorders. While this statement was not, in the absence of any further evidence persuasive of utility or enablement, the subsequent art, in the form of Nakabayashi et al. , has shown the statement to be at least partially true; the human α2/β1 binds with high affinity to TSH receptors, and therefore has diagnostic utility for thyroid imaging, at least. However, no activity was specifically disclosed in the specification as filed, and the protein surely has other activities than binding TSH receptor.

It is noted that applicants point to the specification at page 103, lines 25-29 for basis for the newly added limitation "capable of regulating thyroidal function or promoting thyroid differentiation or proliferation". The specification does not enable the β10 subunit, nor any variant thereof, as having such activity. As stated above, it is believable that α2/β10 binds TSH receptor. Further, the specification at page 9 states that transgenic mice that *overexpress both* α2 and β10 show bilateral thyroid enlargement with multiple follicular papillary adenomas and resultant hyperthyroidism. However, there is no nexus between this result and the specifically

recited regulation of thyroidal function, promotion of thyroid differentiation, or promotion of thyroid proliferation (it is also not clear what "thyroid proliferation" means- generation of additional thyroid glands?). According to Stedman's online dictionary, adenoma is defined as "A benign epithelial neoplasm in which the tumor cells form glands or glandlike structures; usually well circumscribed, tending to compress rather than infiltrate or invade adjacent tissue." Therefore, the experimental observation does not support the specific activities now recited in the claims. It remains that the only specific activity which is supported is the ability to bind TSH receptors.

Claims 1-8, 10, 11, 47-51, 61 and 65 remain rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record in the first office action on the merits, mailed 11/21/2002.

Applicants arguments, filed 9/17/2004, have been fully considered but are not deemed persuasive. Applicants argue that The amendment of the claims to limit to 75% identity is commensurate in scope with the disclosure because 80% of SEQ ID NO: 1 encodes the mature protein. This argument has been fully considered but is not deemed persuasive because the variation in the claimed nucleic acids is not limited to that in the non-coding regions of SEQ ID NO: 1, hence applicants argument is not pertinent to the grounds of rejection. Applicants also argue that the species are adequately described in view of the decision in *Enzo Biochem,Inc. v. Gen-Probe,* 296 F.3d 1316. This argument has been fully considered but is not deemed persuasive because the considerations in this case are entirely different from those in *Enzo*; the *Enzo* case is one in which the nucleic acids were useful as specific hybridization probes, which allowed the discrimination of to *N. gonorrhoeae* from *N. meningitides.* As the utility therein pertains to hybridization, and the utility herein pertains to the ability to bind TSH receptor, the fact situations are non-analogous. Given the unpredictability in the art, the Examiner maintains that merely disclosing that a certain type of variation is envisioned (70% identity, allelic variants, etc.) is not a description of such. Further, comparison to the previously known glycoprotein

hormone subunits is not probative, in view of Nakabayashi et al.'s disclosure that α2 and β10 do not function in concert with the previously known subunits.

At page 10, applicants argue that TSH-like activity, "and other significant activities" are fully described in the specification as originally filed. This argument has been fully considered but is not deemed persuasive because while Nakabayashi et al. have substantiated that α2/β10 binds to TSH receptors, it remains unpredictable what, and if any which disorders are related to α2/β10. Nakabayashi et al. teach that the physiological role of α2/β10 is expected *not* to be the same as TSH, based upon expression patterns. Accordingly, any allusion to disorders that may be treated using such is a mere invitation to experiment to find such disorders.

Claim Rejections - 35 USC § 102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 4-5, 7 and 11 remain rejected under 35 U.S.C. 102(b) as being anticipated by, or in the alternative under 35 U.S.C. § 103(a) as being obvious over G.G. Mahairas et al., Locus AQ495547 disclosed 4/28/99 for reasons of record. Applicants traversal that the reference does not teach a nucleic acid that would encode a protein with the newly recited activity has been fully considered but is not deemed persuasive; see part (d) of claim 2.

Conclusion

No claim is allowed.

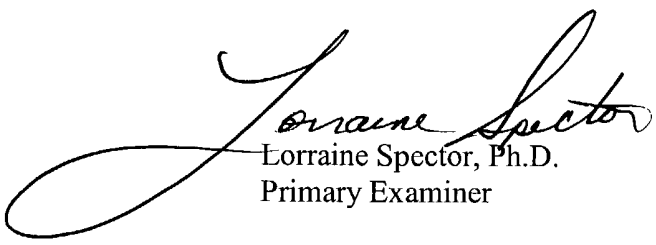
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. ***Effective 1/21/2004, Dr. Spector's telephone number is 571-272-0893.***

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to 571-273-8300. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Lorraine Spector, Ph.D.
Primary Examiner

12/22/2004